"Tao") and Stevenson *et al.* (Annals New York Acad. Science 772:212 [1995]; hereinafter "Stevenson").

1) THE CLAIMS ARE DEFINITE

The Examiner has rejected Claims 1-6 as allegedly being indefinite on two grounds. First, the Examiner argues that Claims 1 and 2 are indefinite "in that it is not clear if the multivalent vaccine is a molecule that comprises 2 Ig variable regions or is a composition which comprises different Ig molecules" (Office Action, page 2). Applicant respectfully disagrees. The specification defines "multivalent vaccine" on page 22, lines 16-23, explaining, in part, that "a vaccine which contains two or more immunoglobulin molecules derived from a B-cell lymphoma where the immunoglobulin moleces differ from one another by at least one idiotope (e.g., these immunoglobulines are somatic variants of one another) is a multivalent vaccine." The phrase "recombinant variable regions of immunoglobulin molecules" is also defined in the specification at page 22. However, in order to further Applicant's business interests and without acquiescing to the Examiner's argument, Applicant has amended Claim 1 and cancelled Claim 2. Applicant reserves the right to prosecute the original claims (or similar claims) in the future. Applicant believes that amended Claim 1 is definite, reciting that the at least two recombinant variable regions of immunoglobulin molecules comprise recombinant immunoglobulin molecules that differ by at least one idiotope (i.e., the at least two recombinant variable regions differ by at least one idiotope).

Second, the Examiner argues that Claims 1 and 2 are ambiguous in that it is not clear if the different immunoglobulin molecules are expressed by the same B cells. Applicant must respectfully disagree. The claim states that the recombinant molecules are derived from "B-cell lymphoma cells." The source of any particular molecule is not relevant to an understanding of the claims. For example, page 94 of the specification explains that total cellular RNA isolated from a tumor is used in the generation of recombinant constructs. The tumor comprises different somatic variants. Therefore, in this embodiment, total RNA obtained from the tissue comprises a population of RNA comprising different somatic variants. Thus, a vaccine composition generated using methods described in this embodiment will have molecules derived from multiple cells. For the above reasons, Applicant respectfully requests that this rejection be withdrawn.

2) THE CLAIMS ARE NONOBVIOUS

The Examiner has rejected Claims 1-6 as allegedly being unpatentable in view of Tao and Stevenson. The Examiner's argument admits that "neither of these references teach 2 or more Ig with different idiotypes" (Office Action, page 3). To compensate for this lack of teaching in the cited references, the Examiner argues that "it would have been prima facie obvious to a person of ordinary skill in the art to make a multivalent vaccine with more than one idiotope, as each B cell is known to produce a single species of Ig with a specified idiotope pattern. B cell lymphoma is well known to one of ordinary skill in the art to be a neoplastic condition that results in an abnormal growth and proliferation of B cells which express different idiotypes as a result of the polyclonal nature of the cells. One of ordinary skill in the art would have been motivated to produce a vaccine with more than one idiotype comprising the composition as a polyvalent vaccine is more effective in counteracting or killing of the different cell populations expressing different idiotopes and achieving a better therapeutic benefit" (Office Action, pages 3-4). The Examiner's entire argument rests on unsupported conclusory statements and is improper under the law. Furthermore, even if the Examiner's unsupported conclusion were true, they do not meet the requirements for a showing of prima facie obviousness because the references do not teach that one skilled in the art should make such vaccines or how one would make such vaccines. The cited references also do not teach cloning of a plurality of sequences representing different idiotypes and demonstration of expression of the plurality of different constructs.

A) The Examiner's arguments are improper as relying on unsupported conclusory statements

The Examiner's argument is based on the following alleged facts:

1) Each B cell is known to produce a single species of Ig with a specified idiotope pattern;
2) B cell lymphoma is well known to be a neoplastic condition that results in an abnormal growth and proliferation of B cells which express different idiotypes as a result of the polyclonal nature of the cells; and

3) A polyvalent vaccine is more effective in counteracting or killing of the different cell populations expressing different idiotypes and achieving a better therapeutic benefit.

The Examiner fails to provide any support for any of these alleged facts, as required by law. In particular, the Examiner has not provided any evidence to support the argument that "a polyvalent vaccine is more effective in counteracting or killing of the different cell populations expressing different idiotypes and achieving a better therapeutic benefit." More particularly, the Examiner has not provided any evidence to support this argument with respect to B-cell lymphoma. The Examiner simply makes a modification to the cited references to supply an element admittedly lacking from these references (that neither of the cited references teach 2 or more Ig with different idiotypes). The requirement that the Examiner make a showing of a suggestion, teaching or motivation to modify the prior art references is "an essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998). There are three sources for this evidentiary component: the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). The suggestion most often comes from the teachings of the pertinent references. *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998). Nonetheless, regardless of the source of the requisite evidence, the Examiner's showing "must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999). Importantly, since an Examiner is NOT one skilled in the art (under the law), the Examiner's opinion on what one skilled in the art might believe does not count. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art."). Of course, if the Examiner has knowledge of relevant facts which are used to make the rejection, the Examiner is free to use those facts - but only if submitted in the form of an affidavit. *See* 37 CFR 1.107(b). In the present case, the Examiner has submitted no such affidavit. Indeed, the Examiner has provided only the Examiner's opinion and conclusory statements--this is not the requisite "evidence" required under the law to support a modification of the prior art. Applicant requests that the Examiner provide a reference or affidavit that provides a teaching

that a polyvalent vaccine for B-cell lymphoma is more effective in counteracting or killing different cell populations expressing different idiotypes and achieving a better therapeutic benefit.

To the extent the cited references address the issue of using a multivalent vaccine versus a vaccine derived from a single (i.e., the predominant) tumor-related sequence, they clearly indicate that multivalent vaccines are not necessary and need not pursued. For example, Stevenson, page 213, states:

> "For certain B cell tumors, such as follicular lymphoma, which may continue to be exposed to the somatic mutation mechanism following neoplastic transformation, a degree of intraclonal mutational heterogeneity is known to occur . . . However, we do not consider that this presents a problem for vaccination for two reasons: first, there was usually a predominant sequence, and second changes in most or all of the idiotypic determinants would be necessary to allow escape of tumor cells from a polyclonal immune attack. For vaccine design, we have chosen to assemble the predominant tumor-related sequence . . ."

Neither references provides any evidence that "a polyvalent vaccine is more effective in counteracting or killing of the different cell populations expressing different idiotypes and achieving a better therapeutic benefit." Thus, one skilled in the art, following the teachings of the cited references, would not be led to the compositions of the presently claimed invention.

B. Even if the Examiner's unsupported statements were taken as true, the cited references do not teach <u>how</u> one would generate the compositions of the presently claimed invention

Even if one were led to generate a multivalent vaccine based on the teachings of Tao and Stevenson (Applicant asserts that there is no such motivation), the cited references do not teach how one could successfully carry out such methods. The present invention provides guidance for generating a multivalent vaccine that reflects the degree of somatic variation found within a patient's tumor. An example of this method is provided in Example 10 of the present specification. Experiments conducted during the development of the present invention identified amplification primers and primer target sites that allow the diverse variable regions of somatic variants to be amplified and cloned together to generate a multivalent vaccine. A protocol for conducting these methods is provided in Example 10, page 94-103. Tao and Stevenson provide no teaching or suggestion that such methods should be conducted or how

one would carry out such methods. Because Tao and Stevenson do not teach the modification suggested by the Examiner and because Tao and Stevenson do not provide any teaching on how one would generate multivalent vaccines, prima facie obviousness has not been established. For the above reasons, Applicant respectfully requests that this rejection be withdrawn.

Applicants assert that new Claims 25-32 are also free of the prior art. New Claims 25-29 recite compositions made by novel methods. Each of the methods recited in these claims is directly from issue methods claims in related U.S. Pat. No. 5,972,334, with the exception of new Claims 26 and 27, which recite minor variations on the corresponding issued claims (Claims 26 and 27 are dependent on Claim 25, which is identical to issued claims, and are therefore also free of the prior art). New Claim 30, recites a multivalent vaccine composition made by a method comprising the step of amplifying cDNA for the variable regions from mRNA from the B-cell lymphoma cells using amplification primers complementary to conserved sequences flanking the variable regions (*See e.g.*, Example 10 for one such embodiment).

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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MARKING SHOWING AMENDMENTS TO THE CLAIMS

1. (Amended) A multivalent vaccine composition comprising at least two recombinant variable regions of immunoglobulin molecules derived from B-cell lymphoma cells, wherein said at least two variable regions comprise recombinant immunoglobulin molecules that differ [cells express at least two different immunoglobulin molecules, said immunoglobulin molecules differing] by at least one idiotope.

3. (Amended) The vaccine composition of Claim 1 [Claim 2], wherein said recombinant immunoglobulin molecules are covalently linked to an immune-enhancing cytokine.

4. (Amended) The vaccine composition of Claim 3, wherein said cytokine is selected from the group consisting of granulocyte-macrophage colony stimulating factor, interleukin-2 and interleukin-4.

5. (Amended) The multivalent vaccine composition of Claim 1 further comprising at least one pharmaceutically acceptable excipient.

6. (Amended) The multivalent vaccine composition of Claim 1 further comprising an adjuvant.